REMARKS

Claims 99-100, 103-107, 109-110, 113-117, 119 and 121 were previously pending.

Applicants have amended claim 99 to recite "A method for enhancing uptake of an oligonucleotide into a lung of a mammal, said method comprises: administering an aerosolized oligonucleotide into the lung of a mammal, wherein the aerosol particles have a size of about 1 to about 5 microns, wherein said oligonucleotide is 8 to 30 nucleotides in length, wherein at least one nucleoside in said oligonucleotide is a 2'-O-methoxyethyl nucleoside, wherein each cytosine of said oligonucleotide is a 5-methylcytosine, wherein said oligonucleotide is taken up by at least one cell type in the lung of the mammal, and wherein the amount of said oligonucleotide taken up by said cell type in the lung of the mammal is enhanced as compared to an oligonucleotide with the same sequence and lacking said 2'-O-methoxyethyl nucleoside."

Applicants have added new claim 128.

Applicants have amended claims 100 and 110 to recite "at least one internucleotide linkage within said oligonucleotide is a phosphorothioate linkage."

Support for these amendments can be found throughout the specification as filed, for example, at Example 3. Applicants submit that no new matter is added and request entry of these amendments. After entry of these amendments, claims 99-100, 103-107, 109-110, 113-117, 119, 121 and 128 will be pending and under consideration.

Claim Objections

Claims 107 and 117 are objected to as being a substantial duplicate of claims 100 and 110, respectively. Applicants have amended claims 100 and 110 to recite "at least one internucleotide linkage within said oligonucleotide is a phosphorothioate linkage." Applicants request withdrawal of this objection.

35 U.S.C. § 103(a) – Obviousness

Claims 99, 100, 103-107, 109, 110, 113-117, 119, and 121 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Nyce *et al.*, (WO 96/40266) in view of Nicklin *et al.* (WO 98/09633) and Levesque *et al.*, (Mol. Pharmacol., 51, 1997, 209-216). *Office Action* at 3. The Office asserts that Nyce discloses the invention with the exception of 2'-O-methoxyethyl and 5-

methylcytosine modifications. *See Office Action* at 6. The Office asserts that Nicklin and Levesque disclose the missing elements, that it would have been obvious to modify the antisense of Nyce to include the modifications of Nicklin and Levesque, and that the level/degree of modification amounts to routine optimization. Applicants respectfully traverse.

Lack of a prima facie case

In response to Applicants' previous arguments, the Office asserts that "[i]t was known in the art to deliver modified antisense compounds via aerosol delivery, each of the modifications were known to enhance the delivery of antisense compounds…," and that "each of the instantly recited chemical modifications were known in the art to benefit the stability of antisense oligonucleotides," as evidenced by the cited references. *Office Action* at 7 and 9, (emphasis added).

Applicants respectfully submit that neither of these statements are supported by the evidence of record, and therefore are a statement by "official notice." *See, e.g., In re Zurko*, 258 F.3d 1379, 1385, 59 USPQ2d 1693, 1697 (Fed. Cir. 2001); and *In re Ahlert*, 424 F.2d 1088, 1091, 165 USPQ 418, 420 (CCPA 1970).

To the contrary, as noted previously, none of the portions of the references cited by the Office disclose that the 2'-MOE or 5'-methylcytosine modifications enhance delivery or benefit the stability of antisense oligonucleotides. The only evidence of record regarding whether one of skill in the art would have expected 2'-MOE modifications to enhance delivery or benefit the stability of antisense oligonucleotides modifications is the expert declaration of Dr. Richard Geary, previously attached as Exhibit 1. In paragraph 4 of his declaration, Dr. Geary states:

> I have reviewed Nicklin et al. and do not find support for the assertion that incorporation of 2'-O-methoxyethyl modifications would result in increased uptake of a nucleic acid into cells.

Further, Dr. Geary states that

> [A]t the time of the invention, one in the field would not have expected the inclusion of 2'-O-methoxyethyl modifications to improve the uptake of nucleic acids into a cell of the lung. *Geary Declaration* at ¶5 (emphasis added).

Thus, the statements of the Office that 2'-MOE modifications are known to increase uptake and enhance stability are in direct conflict with the evidence of record. In accordance with M.P.E.P. §2144.03C, Applicants respectfully request documentary evidence demonstrating

that one of skill in the art would recognize that adding 2'-MOE and 5'-methylcytosine modifications enhance delivery or benefit the stability of antisense oligonucleotides. Absent additional evidence, these assertions cannot serve as a basis for concluding that the claims are obvious.

The Office also asserts that with regard to the level/degree of modification, "it would have been prima facie obvious to perform routine optimization to determine the optimal level of modification as well as the optimal dosage, as noted in *In re Aller*, 105 USPQ 233 at 235." *Office Action* at 6. Applicants respectfully traverse.

An allegation based on routine experimentation does not, by itself, provide a legally sufficient reason to pursue a claimed limitation. The issue of whether one could have routinely performed the required modifications is inapposite. The mere *ability* of a person skilled in the art to perform a modification does not provide a *reason* to pursue that modification. There is no evidence of record establishing that the amount of 2'-MOE or 5'-methylcytosine modification is a result-effective variable for enhancing uptake of an oligonucleotide in the lung, such that the variable is subject to obvious optimization. A particular parameter must first be recognized as a result-effective variable, *i.e.*, a variable which achieves a recognized result, before the determination of the optimum or workable ranges of the variable might be characterized as routine experimentation. *See M.P.E.P. § 2144.05.II.B*; *see also In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977). This is particularly the case if one skilled in the art is faced with a large number of possible modifications. In the instant case, one skilled in the art would have, indeed, been faced with many possible modifications including, but not limited to, a multitude of chemical modifications to the sugar, base and internucleoside linkage known at the time as disclosed by Nicklin and Nyce. As noted above, the references teach that there may be advantages with numerous modifications but none of the cited references teach specifically that 2'-MOE or 5'-methylcytosine modifications enhance stability or uptake. As such, it would not be a matter of routine optimization of the teachings of the cited references to vary the level/degree of 2'-MOE or 5'-methylcytosine modifications to improve uptake of the oligonucleotide. Thus, absent additional evidence, the assertion of obvious optimization cannot serve as a basis for concluding that the claims are obvious.

For at least these reasons, Applicants submit that the Office lacks an evidentiary basis to support a *prima facie* case of obviousness. Therefore, Applicants request withdrawal of the rejection of the pending claims under 35 U.S.C. § 103(a).

Unexpected Results

In addition, even if a *prima facie* case of obviousness has been established, a point which Applicants do not concede, Applicants submit that the claimed method provides unexpected results which are sufficient to overcome any *prima facie* case of obviousness. Applicants have found that incorporating 2'-O-methoxyethyl (2'-MOE) nucleosides enhances the uptake of oligonucleotides into cells of the lungs when administered into the lung. Tables 2 and 3 of Example 3 show the concentration of oligonucleotide in the lungs of mice following single and multiple administrations, respectively, of three antisense molecules. Importantly, ISIS 15163 performs more than 300% better than ISIS 17009.

As the Examine correctly notes, ISIS 15163 has a phosphodiester backbone while ISIS 17009 has a fully phosphorothioate backbone. Applicants and the Geary Declaration incorrectly stated that the only difference between the molecules was the inclusion of 2'-O-methoxyethyl nucleosides in ISIS 15163. Applicants apologize for any confusion created by previous statements that did not point out the difference in backbone.

However, as Nyce et al. teaches, at the time of the invention it was understood that phosphodiester backbones were not as stable as phosphorothioate backbones. *See, e.g., Nyce* at page 7, line 22 through page 8, line 18. Therefore, at the time of the invention, one of skill in the art would have expected ISIS 17009, with a fully phosphorothioate backbone, to be more stable than ISIS 15163, which has a phosphodiester backbone. To the extent that the stability of the oligonucleotide would be expected to affect uptake, the more stable compound, ISIS 17009 would have been expected to have improved uptake. This makes Applicants' results even more surprising and unexpected, since the addition of 2'-O-methoxyethyl modifications improved uptake in the absence of a phosphorothioate backbone as compared to the same sequence with a fully phosphorothioate backbone.

The Office responds to Applicants' assertion of unexpected results with three arguments: (1) that improved cellular uptake is not a limitation of the claims, some level of uptake is

expected based on the cited references, that "it is not unexpected for oligonucleotides with the instant combinations to result in uptake," and therefore demonstration of unexpected results requires "some teaching that sets forth that this combination would likely not result in uptake;" (2) the declaration of Dr. Geary is not persuasive because "[t]he statement concentrates on improved cellular uptake, which is not an element of the instant claims and does not set forth what the improvement is in comparison to;" and, (3) that the unexpected results are not commensurate in scope with the instant claims. *Office Action* at pages 10 and 11.

Regarding the Office's first argument, Applicants remind the Office that unexpected results do not need to be recited in the claims. If the unexpected properties of a compound or method must always be recited in a claim, they would not be "secondary considerations" which can overcome a *prima facie* case of obviousness, but rather would always be limitations which are considered as part of the *prima facie* case. *See, e.g. M.P.E.P. §2145.* Rather, the unexpected results that flow from the claimed composition or method need only be unexpected in view of the closest cited reference. *See M.P.E.P. §716.02.* Thus, the relevant question is not whether it is expected for the recited oligonucleotides "to result in uptake," or if there is some teaching that the recited combination "would likely not result in uptake." The relevant question is whether the level of uptake demonstrated in Example 3 of the instant specification is unexpected in view of the closest reference.

Nevertheless, in the interest of advancing prosecution, Applicants have amended claim 99 to recite: "A method for enhancing uptake of an oligonucleotide…wherein the amount of said oligonucleotide taken up by said cell type in the lung of the mammal is enhanced as compared to an oligonucleotide with the same sequence and lacking said 2'-O-methoxyethyl nucleoside."

As stated above, there is no evidence to support the Office's assertion that increased uptake was a known and expected benefit of the inclusion of 2'-O-methoxyethyl modifications. In fact, the evidence of record states that the opposite – improved uptake by inclusion of one or more 2'-MOE modifications is an unexpected property. The declaration of Dr. Geary, an established expert in the field with more than 14 years of experience establishes that 2'-MOE modifications were expected to improve target binding affinity, but not uptake, and therefore the results of Example 3 were unexpected at the time of the invention:

> 4. I have reviewed Nicklin et al. and do not find support for the assertion that incorporation of 2'-O-methoxyethyl modifications would result in increased uptake of a

nucleic acid into cells. Rather, Nicklin et al. teach that modification of the 2' position of the nucleotide sugar increases target binding affinity. *Nicklin* at page 3.

5. It is my expert opinion that at the time of the invention, one of skill in the art would not have expected the inclusion of 2'-O-methoxyethyl modifications to improve the uptake of nucleic acids into a cell of the lung. At the time of the invention, the inclusion of one or more, a majority, or even full 2'-O-methoxyethyl modifications in a nucleic acid was regarded as a relatively minor change to the overall chemistry of an oligonucleotide and was not thought to alter the overall biochemical characteristics of the molecule. ...

6. The fact that the inclusion of 2'-O-methoxyethyl modifications improved cellular uptake into cells of the lung is demonstrated by the results of Table 2 and 3 of the above-captioned application. ... It is my expert opinion that at the time of the invention, this result was unexpected. *Geary Declaration* at ¶¶4-6 (emphasis added).

Therefore, Applicants have established that at the time of the invention, the results of improved uptake by inclusion of 2'-O-methoxyethyl modifications was unexpected in view of the Nicklin *et al.* reference relied on by the Office.

Regarding argument (2), the Office rejects the Geary Declaration because "[t]he statement concentrates on improved cellular uptake, which is not an element of the instant claims and does not set forth what the improvement is in comparison to." *Office Action* at page 11. Applicants have already addressed the first point – unexpected results do not have to be recited in the claims for them to be considered, they are "secondary considerations" which rebut a *prima facie* case of obviousness. *See M.P.E.P. §2145.* Nevertheless, in the interest of advancing prosecution, Applicants have amended claim 99 to recite: "A method for enhancing uptake of an oligonucleotide...wherein the amount of said oligonucleotide taken up by said cell type in the lung of the mammal is enhanced as compared to an oligonucleotide with the same sequence and lacking said 2'-O-methoxyethyl nucleoside and 5-methylcytosine."

With respect to the second criticism, that the declaration does not set forth what the improvement is in comparison to, Applicants respectfully submit that the declaration is clear – inclusion of 2'-O-methoxyethyl modifications improves uptake in the lung as compared to oligonucleotides which do not include the modifications. *See Geary Declaration* at ¶¶5 and 6. Thus, the Office's rejection of the Geary Declaration lacks any factual basis. Applicants remind the Examiner that "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; ..." *M.P.E.P. §2107.*

Finally, Applicants address the Office's assertion that the unexpected results are not commensurate in scope with the instant claims, stating that "the instant claims require a combination of all three of these types of modifications [phosphorothioate, 5-methylcytosine and 2'-MOE] and thus the example pointed to by applicant is not representative of the instant genus." *Office Action* at page 11. Applicants respectfully submit that the examples relied on are sufficient to support the full scope of the pending claims.

Applicants have demonstrated enhanced uptake in the absence of a phosphorothioate backbone (*see Example 3*). Therefore, currently pending claim 99, which does not require a phosphorothioate modification, is commensurate in scope with the example with respect to this modification. In addition, had the 2'-MOE modified oligonucleotide tested in Example 3 also had a phosphorothioate backbone, the uptake would be expected to be even greater, given that phosphorothioate modifications were known to enhance stabilization, as discussed above. Therefore, a skilled artisan would view the recitation of phosphorothioate modification in dependent claims 100, 107, 110, 117 as commensurate in scope with the examples.

With respect to 5-methylcytosine modification, Applicants demonstrated enhanced uptake of a compound wherein each cytosine was a 5-methylcytosine. Claim 99, and all the claims which depend therefrom, requires that each cytosine is a 5-methylcytosine. Thus, with respect to this modification, the claims are commensurate in scope with the example.

Finally, with respect to 2'-MOE modifications, Applicants have shown that the inclusion of 2'-MOE modifications increases the uptake of oligonucleotides administered into the lung as compared to an oligonucleotide with the same sequence but lacking 2'-MOE modifications. As discussed above, this result is unexpected at <u>any</u> level of enhanced uptake – 2'-MOE modifications were not known or expected to increase uptake of oligonucleotides in the lung. Thus, while Table 3 shows as much as a 356% increase in uptake when all nucleosides comprise a 2'-MOE modification, this level of enhanced uptake is not required for the entire claim scope. Applicants submit that in view of Applicants' disclosure, one of skill in the art would recognize while fewer 2'-MOE modifications may result in less of an effect, the inclusion of any 2'-MOE modification would enhance uptake. Claim 99 requires that the oligonucleotide include at least one 2'-MOE nucleoside, and thus are commensurate in scope with the unexpected result – enhanced uptake into the lung.

Nevertheless, in the interest of advancing prosecution, Applicants have amended claim 99 to recite: "A method for enhancing uptake of an oligonucleotide...wherein the amount of said oligonucleotide taken up by said cell type in the lung of the mammal is enhanced as compared to an oligonucleotide with the same sequence and lacking said 2'-O-methoxyethyl nucleoside and 5-methylcytosine." Thus, Applicants submit that the pending claims are commensurate in scope with the unexpected results of enhanced uptake of the oligonucleotide into the lung.

In summary, Applicants submit that the cited references do not teach that the inclusion of 2'-MOE modifications would enhance cellular uptake of an aerosolized oligonucleotide delivered into the lung. Thus, even *if* the Office has established that one of skill in the art would have been motivated to include a 2'-MOE modification in the method of Nyce, a point Applicants do not concede, Applicants submit that the evidence of record establishes that the increased cellular uptake of the recited compounds is unexpected, and therefore the pending methods are not obvious in view of the cited references.

For at least the above reason, Applicants submit that the pending claims are patentable over cited references. Applicants therefore request withdrawal of the rejection of the pending claims under 35 U.S.C. § 103(a).

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

Patents and Applications

Applicants wish to draw the Examiner's attention to the following patents or applications. Applicants encourage the Examiner to review and monitor the prosecution of the following patents and/or applications throughout the pendency of this application.

Patent / Serial Number	Title	Issued / Filed
09/083,586	COMPOSITIONS AND METHODS FOR THE PULMONARY DELIVERY OF NUCLEIC ACIDS	5/21/1998

CONCLUSION

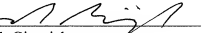
In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 9/9/10

By: 

Brenden S. Gingrich
Registration No. 60,295
Attorney of Record
Customer No. 55,389
(858) 836-9000